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ORIGINAL SCIENTIFIC REPORT

Implications of Intrahepatic Cholangiocarcinoma Etiology on Recurrence and Prognosis after Curative-Intent Resection: a Multi-Institutional Study

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Abstract

Background We sought to investigate the prognosis of patients following curative-intent surgery for intrahepatic cholangiocarcinoma (ICC) stratified by hepatitis B (HBV-ICC), hepatolithiasis (Stone-ICC), and no identifiable cause (conventional ICC) etiologic subtype.

Methods 986 patients with HBV-ICC ($n = 201$), stone-ICC ($n = 103$), and conventional ICC ($n = 682$) who underwent curative-intent resection were identified from a multi-institutional database. Propensity score matching (PSM) was used to mitigate residual bias.

Results HBV-ICC patients more often had cirrhosis, earlier stage tumors, a mass-forming lesion, well-to-moderate tumor differentiation, and an R0 resection versus stone-ICC or conventional ICC patients. Five-year recurrence-free survival among HBV-ICC and conventional ICC patients was 23.9 and 17.8%, respectively, versus a recurrence-free of only 8.3% among patients with stone-ICC. Similarly, 5-year overall survival among patients with stone-ICC was only 18.3% compared with 48.9 and 38.0% for patients with HBV-ICC and conventional ICC, respectively. On PSM, patients with stone-ICC group had equivalent long-term outcomes as HBV-ICC patients. In contrast, on PSM, stone-ICC patients had a median overall survival of only 18.0 months versus 44.0 months for patients with conventional ICC. Median overall survival after intrahepatic-only recurrence among patients who had stone-ICC (6.0 months) was worse than OS among HBV-ICC (13.0 months) or conventional ICC (12.0 months) ($p = 0.006$ and $p = 0.082$, respectively).

Conclusions While HBV-ICC had a better prognosis on unadjusted analyses, these differences were mitigated on PSM suggesting no stage-for-stage differences in outcomes compared with stone-ICC or conventional ICC. In contrast, patients with stone-ICC had worse long-term outcomes. These data highlight the relative importance of ICC etiology relative to established clinicopathological factors in the prognosis of patients with ICC.

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Introduction

Intrahepatic cholangiocarcinoma (ICC) is the second most common primary liver malignancy after hepatocellular carcinoma (HCC), accounting for 10–15% of all primary liver cancers [1, 2]. Although relatively rare, the incidence of ICC is gradually increasing worldwide [2, 3]. The incidence of ICC has a wide geographical variation and is less common in the West versus East Asia where the incidence can be as high as 71/100,000 [2, 4]. The reason for this varied incidence may be due to differences in causative risk factors for ICC among Western versus Eastern patients [5]. For example, in the West, primary sclerosing cholangitis (PSC), primary biliary cirrhosis (PBC), and hepatitis C (HCV) are the most common risk factors for ICC; in contrast, in Eastern countries, hepatitis B (HBV), hepatolithiasis, as well as hepatic parasite infection are the major causes of ICC [2, 6–8]. Although an association among these risk factors and ICC has been established by epidemiologic investigation, many cases of ICC develop in the absence of known etiological factors [9, 10].

Surgical resection remains the only potentially curative treatment for ICC, yet only 20–40% of patients with ICC are potential surgical candidates [11–13]. Compared with a 5% survival for inoperable patients, 5-year survival after curative resection of ICC ranges from 20 to 35% [14, 15]. Data on prognosis following resection have focused on tumor-specific factors such as lesion size and number, as well as vascular invasion and lymph node status. In contrast, only a handful of studies have investigated the relative impact of ICC etiology on long-term survival following resection of ICC, and these data conflict [16–21]. For example, HBV infection has been reported to be a favorable prognostic factor after hepatic resection of ICC in some studies, but not others [16–21]. Similarly, patients with hepatolithiasis-related ICC have been reported to have worse outcomes compared with patients who had non-hepatolithiasis-associated ICC or HBV-ICC in some studies, but similar or even favorable prognosis in other reports [16, 18, 22–24]. Previous reports have been limited, as all were single center studies with a small number of patients. In addition, previous studies were largely based on patients exclusively from either the West or the East. As such, the objective of the current study was to investigate the impact of ICC etiology on the prognosis of patients following resection of ICC using a large, multi-institutional, international database. In addition, we sought to define recurrence, as well as post-recurrence prognosis following curative-intent surgery stratified by ICC etiology subtype.

Materials and methods

Study population and design

A multi-institutional database that included 15 major hepatobiliary centers in the USA, Europe, Australia, and Asia was utilized to identify 1036 patients who underwent curative-intent hepatic resection for ICC from 1990 to 2016. The 15 medical centers included The Ohio State University, Columbus, OH; Stanford University, Stanford, CA; University of Virginia, Charlottesville, VA; Emory University, Atlanta, GA; Fundeni Clinical Institute of Digestive Disease, Bucharest, Romania; Johns Hopkins Hospital, Baltimore, MD; Curry Cabral Hospital, Lisbon, Portugal; Ospedale San Raffaele, Milan, Italy; Royal Prince Alfred Hospital, University of Sydney, Sydney, Australia; Eastern Hepatobiliary Surgery Hospital, Shanghai, China; Beaujon Hospital, Clichy, France; University of Ottawa, Ottawa, Ontario, Canada; Erasmus University Medical Centre, Rotterdam, Netherlands; University of Verona, Verona, Italy; and Yokohama City University School of Medicine, Yokohama, Japan. All patients were diagnosed with ICC confirmed by histological examination. The Institutional Review Boards of each participating institution approved the study.

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Based on the known causative factors of ICC, patients were divided into HBV-associated ICC (HBV-ICC, $n = 201$); hepatolithiasis-associated ICC (Stone-ICC, $n = 103$); HCV-associated ICC (HCV-ICC, $n = 15$); HBV + HCV-ICC ($n = 7$); hepatitis + stone-ICC ($n = 13$); distomatosis hepatitis-associated ICC (fluke-ICC, $n = 15$); and ICC with no attributable cause (conventional ICC, $n = 682$). Due to the small number and heterogeneity of patients with HCV-ICC, HBV + HCV-ICC, hepatitis + stone-ICC, and fluke-ICC, these patients were excluded ($n = 50$). In turn, 986 patients were included in the final analytic cohort stratified as HBV-ICC, stone-ICC, and conventional ICC.

Data collection and follow-up

Standard demographic, perioperative clinicopathological, and tumor-related characteristics were collected. Tumor characteristics were based on final pathology reports including liver cirrhosis, tumor size, tumor number, tumor morphology, vascular/perineural/biliary/adjacent organ invasion, lymph node metastasis, and histological grade. Data on tumor stage were collected according to the American Joint Committee on Cancer (AJCC) 7th edition staging system [25].

After the initial operation, patients were regularly followed with serum CA19-9, CEA, and abdominal CT or MRI. Recurrence was defined as the presence of a biopsy-proven tumor or an image showing a suspicious lesion. Recurrence was classified as intrahepatic, extrahepatic, or both intra- and extrahepatic. Recurrence time interval was calculated from the date of the first surgery to the date of recurrence. Overall survival (OS) and recurrence-free survival (RFS) were calculated from the date of surgery. OS after the first recurrence was calculated from the date of recurrence.

Treatment of recurrence

Patients with recurrence were evaluated for future treatments based on tumor location, tumor number, general performance status, and liver function. Curative-intent therapies including surgical re-resection, ablation, or combined resection plus ablation were considered for patients with intrahepatic-only recurrence. Palliative treatments such as intra-arterial therapies (IAT), chemotherapy, and chemoradiation were considered for patients with advanced recurrent disease. Patients with advanced recurrence, poor liver function, or severe medical comorbidities received best supportive care (BSC).

Statistical analysis

Continuous variables were expressed as medians with interquartile ranges (IQR) and compared with Mann–Whitney U test or the Kruskal–Wallis test as appropriate. Categorical variables were expressed as number and percentages and compared by Chi squared test or Fisher's exact test. OS and RFS rates were calculated by the Kaplan–Meier method and compared using log-rank tests. In all analyses, a two-tailed p value <0.05 was considered statistically significant. Bonferroni correction was applied for the comparison of clinical characteristics, recurrence patterns and treatments, as well as OS and RFS among the HBV-ICC, stone-ICC, and conventional ICC patients (significance threshold, $p = 0.05$ divided by the number of groups: $p = 0.017$). Propensity score matching (PSM) was used to mitigate residual bias using variables potentially affecting long-term outcomes in logistic regression analysis. Propensity score analysis with 1:1 matching was performed within a range of 0.05 of standard deviation. Statistical analysis was carried out using SPSS 22.0 (Chicago, IL, USA).

Results

Baseline characteristics

The clinicopathological characteristics of HBV-ICC ($n = 201$, 20.4%), stone-ICC ($n = 103$,10.4%) and conventional ICC ($n = 682$, 69.2%) patients are summarized in Table 1. Patients with stone-ICC had similar clinicpathological characteristics as patients who had conventional ICC with regard to age, gender, tumor features, type of surgical procedure, as well as incidence of peri-operative complications (all $p > 0.05$). In contrast, patients with HBV-ICC were more often male, younger, and had a higher incidence of underlying hepatic cirrhosis (all $p < 0.001$). In addition, HBV-ICC patients were more likely to have tumors characterized by favorable underlying pathological features including smaller size, and disease that more often was solitary, unilobar, as well as well-to-moderately differentiated (all $p < 0.01$). HBV-ICC patients were also less likely to undergo a major hepatectomy and had lower intraoperative blood loss and decreased perioperative morbidity (all $p < 0.01$). HBV-ICC patients had a higher incidence of an R0 resection (HBV-ICC, 96.5%) than stone-ICC (80.6%) and conventional ICC (85.3%) ($p < 0.001$).

Table 1 Clinicopathologic characteristics of curatively treated patients with intrahepatic cholangiocarcinoma associated with HBV infection, hepatolithiasis, and unknown causes

	HBV-ICC ($n = 201$)	Stone-ICC ($n = 103$)	Conventional ICC ($n = 682$)	P value
Age (years)	52 (45–60)	61 (54–71)	61 (52–69)	<0.001
Male gender	158 (78.6%)	51 (49.5%)	339 (49.7%)	<0.001
Body mass index	24.3 (21.4–27.1)	24.5 (22.8–27.1)	25.6 (22.6–28.5)	0.001
Liver cirrhosis	74 (36.8%)	22 (21.4%)	9 (1.3%)	<0.001
Clinical jaundice	5 (2.4%)	16 (15.5%)	79 (11.6%)	<0.001
CA19-9 (U/mL)	27.3 (13.8–68.7)	93.0 (25.1–528.3)	73.0 (22.0–290.0)	<0.001
CEA (ng/mL)	2.5 (1.6–4.0)	2.8 (1.5–5.1)	2.4 (1.4–4.4)	0.759
ALT (U/L)	28.8 (18.9–43.3)	33.0 (23.0–72.0)	30.0 (20.0–51.0)	0.044
AST (U/L)	28.0 (21.0–38.7)	33.0 (25.5–51.0)	32.0 (23.0–48.0)	0.002
TBIL (μmol/L)	12.0 (8.6–17.1)	12.0 (8.6–17.1)	12.0 (8.6–18.8)	0.997
Albumin (g/L)	41.9 (40.1–45.0)	39.8 (34.8–43.1)	41.3 (38.0–44.0)	<0.001
Hemoglobin (g/L)	141.0 (129.0–150.0)	129.0 (113.7–139.3)	127.0 (116.0–138.0)	<0.001
Platelet count ($\times 10^9$/L)	178.5 (132.0–224.5)	227.0 (177.0–296.5)	228.5 (179.0–289.3)	<0.001
Tumor size (cm)	5.5 (3.8–7.6)	6.0 (3.5–8.8)	6.1 (4.5–9.0)	0.009
Multiple lesions (≥2)	20 (10.0%)	21 (20.4%)	130 (19.1%)	0.008
Bilobar tumor	14 (7.0%)	25 (24.3%)	143 (21.0%)	<0.001
Macrovascular invasion	19 (9.5%)	10 (9.7%)	80 (11.7%)	0.597
Microvascular invasion	35 (17.4%)	27 (26.2%)	212 (31.1%)	<0.001
Perineural invasion	11 (5.5%)	26 (25.2%)	115 (16.9%)	<0.001
Direct invasion of adjacent organs	7 (3.5%)	8 (7.8%)	57 (8.4%)	0.062
Satellite lesions	52 (25.9%)	22 (21.4%)	141 (20.7%)	0.297
AJCC T stage				<0.001
T1-T2	188 (93.5%)	78 (75.7%)	483 (70.8%)	
T3-T4	10 (5.0%)	20 (19.4%)	136 (19.9%)	
Missing	3 (1.5%)	5 (4.9%)	63 (9.2%)	
AJCC N stage				<0.001
N0	167 (83.0%)	51 (49.5%)	323 (47.4%)	
N1-N2	17 (8.5%)	23 (22.3%)	131 (19.2%)	
Nx	17 (8.5%)	29 (28.2%)	228 (33.4%)	
Histological grade				<0.001
Well-to-moderate	184 (91.5%)	73 (70.9%)	522 (76.5%)	
Poor to undifferentiated	13 (6.5%)	25 (24.2%)	130 (19.1%)	
Missing	4 (2.0%)	5 (4.9%)	30 (4.4%)	
Morphological type				<0.001
Mass-forming	194 (96.5%)	83 (80.6%)	510 (74.8%)	
Papillary	1 (0.5%)	7 (6.8%)	19 (2.8%)	
Peri-ductal infiltrating	2 (1.0%)	3 (2.9%)	42 (6.2%)	
Mass-forming + peri-ductal infiltrating	4 (2.0%)	7 (6.8%)	57 (8.4%)	
Missing	0	3 (2.9%)	54 (7.8%)	
Resection procedure				<0.001
Minor resection	157 (78.1%)	35 (34.0%)	202 (29.6%)	
Major resection	44 (21.9%)	68 (66.0%)	480 (70.4%)	
R0 resection	194 (96.5%)	83 (80.6%)	582 (85.3%)	<0.001
Major vascular resection	16 (8.0%)	5 (4.9%)	100 (14.7%)	0.002
Lymphadenectomy	46 (22.9%)	64 (62.1%)	354 (51.9%)	<0.001
Intraoperative blood loss	200.0 (150.0–475.0)	400.0 (250.0–900.0)	500.0 (250.0–900.0)	<0.001
Operation time (min)	115.0 (90.0–150.0)	235.0 (163.5–360.0)	240.0 (171.0–364.8)	<0.001

Table 1 continued

	HBV-ICC ($n = 201$)	Stone-ICC ($n = 103$)	Conventional ICC ($n = 682$)	*P* value
Intraoperative blood transfusion	34 (16.9%)	39 (37.9%)	181 (26.5%)	<0.001
Adjuvant chemo-/radio-therapy	17 (8.5%)	31 (30.1%)	255 (37.4%)	<0.001
Postoperative complications				<0.001
No complication	146 (72.6%)	55 (53.4%)	392 (57.5%)	
Grade I–II	44 (21.9%)	22 (21.4%)	148 (21.7%)	
Grade III–IV	8 (4.0%)	20 (19.4%)	106 (15.5%)	
Grade V	3 (1.5%)	6 (5.8%)	36 (5.3%)	
90-day mortality	8 (4.0%)	10 (9.7%)	41 (6.0%)	0.137

ICC intrahepatic cholangiocarcinoma, *HBV* hepatitis B virus, *Ca19-9* Carbohydrate antigen 19-9, *CEA* Carcinoembryonic antigen, *ALT* alanine aminotransferase, *AST* aspartate aminotransferase *TBIL* total bilirubin, *AJCC* American Joint Committee on Cancer

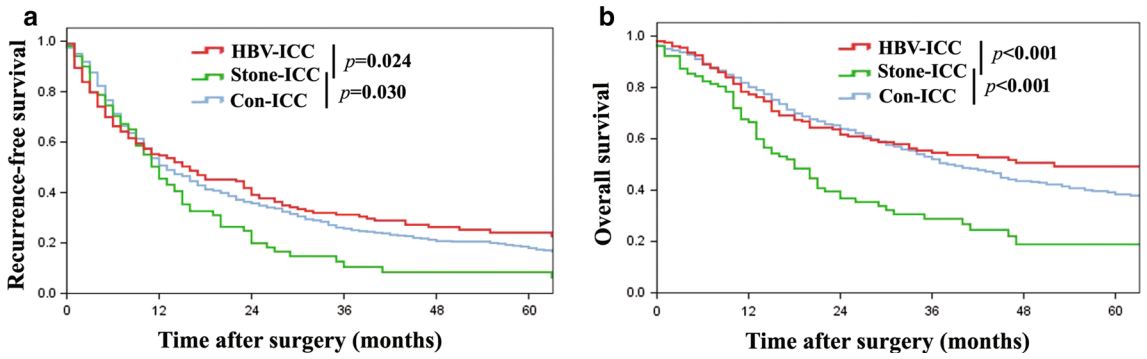

Fig. 1 Comparison of overall survival **a** and recurrence-free survival **b** after curative-intent surgery for HBV-ICC, stone-ICC and conventional ICC. HBV, hepatitis B virus; ICC, intrahepatic cholangiocarcinoma; Con, conventional

Overall and recurrence-free survival

The OS and RFS following initial curative-intent surgery are summarized in Fig. 1. Despite similarities in clinicopathologic factors, patients with stone-ICC had worse long-term outcomes compared with patients who had conventional ICC. In contrast, HBV-ICC patients had the best outcomes. Specifically, 5-year RFS among HBV-ICC and conventional ICC patients was 23.9% and 17.8%, respectively, versus an RFS of only 8.3% among patients with stone-ICC (all $p < 0.05$) (Fig. 1a). Similarly, 5-year OS among patients with stone-ICC was only 18.3% compared with a 5-year OS of 48.9 and 38.0% for patients with HBV-ICC and conventional ICC, respectively (Fig. 1b).

Given the differences in the baseline characteristics among the groups, a 1:1 propensity score matching (PSM) analysis was performed. Using PSM, 80 pairs of patients who had stone-ICC and conventional ICC were identified and matched on demographic data, presence of liver cirrhosis, tumor characteristics, as well as surgical margin and perioperative morbidity (Supplementary Table 1). In the propensity model, median RFS among stone-ICC and conventional ICC patients were 12.0 months and 16.0 months, respectively; 5-year RFS was 7.8 and 26.6%, respectively ($p < 0.01$) (Fig. 2a). In examining OS, patients with stone-ICC had a markedly shorter median OS of 18.0 months versus 44.0 months for patients with conventional ICC; similarly, 5-year OS was 17.8 and 44.4%, respectively ($p < 0.01$) (Fig. 2b).

PSM was also utilized to identify 41 pairs of patients with stone-ICC and HBV-ICC who had comparable baseline clinical and pathologic characteristics (Supplementary Table 2). In the propensity model, patients with stone-ICC had equivalent RFS and OS versus patients with HBV-ICC (median RFS: 12.0 months vs 14.0 months; median OS: 21.0 months vs 27.0 months, both $p > 0.1$, Figs. 2c and d).

Recurrence treatment and outcome

In total, 733 out of the 986 (74.3%) patients developed tumor recurrence after the initial surgical resection. Among patients who recurred, 476 (64.9%) had intrahepatic-only

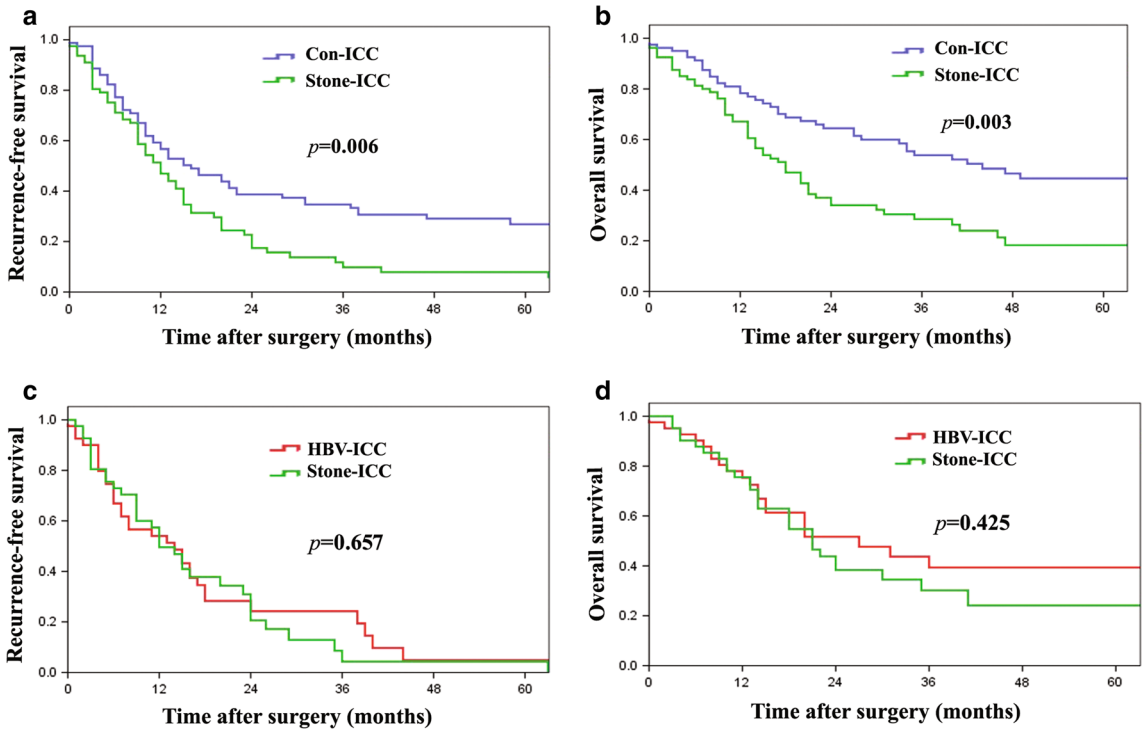

Fig. 2 Comparison of the overall survival and recurrence-free survival between stone-ICC and conventional ICC (**a** and **b**) and between HBV-ICC and stone-ICC (**c** and **d**) after propensity score matching. HBV, hepatitis B virus; ICC, intrahepatic cholangiocarcinoma; Con, conventional

recurrence, while 89 (12.1%) and 168 (22.9%) experienced an extrahepatic or combined intra- and extrahepatic recurrence, respectively. Following the initial resection, the timing and pattern of recurrence were no different among patients who had HBV-ICC, stone-ICC, or conventional ICC (both $p > 0.1$, Fig. 3a and b). For patients with intrahepatic-only recurrence, 115 (24.2%) patients underwent curative-intent treatment of the recurrent tumor, while 269 (56.5%) and 92 (19.3%) patients received palliative treatment or BSC, respectively. Notably, following resection of an initial HBV-ICC or stone-ICC, curative-intent treatment of a recurrence was less common than treatment of a conventional ICC recurrence (both $p < 0.001$, Fig. 3c). In turn, median OS after intrahepatic-only recurrence among patients who had stone-ICC (6.0 months) was worse than OS among HBV-ICC (13.0 months) or conventional ICC (12.0 months) ($p = 0.006$ and $p = 0.082$, respectively, Fig. 4).

Discussion

Different etiologies of ICC may be related to varied and distinct pathogenic mechanisms of disease. While a subset of ICC tumors may be associated with a specific etiologic factor (i.e. HBV, stones, etc.), most ICC tumors occur sporadically without a known risk factor—which was defined as conventional ICC in the present study [9, 10]. Predisposing factors such as chronic hepatitis viral infection and hepatolithiasis can be, however, important causes of ICC in highly endemic areas [26]. The current study was important because it defined the clinicopathological characteristics, as well as prognosis, recurrence, and post-recurrence outcomes of patients following curative-intent resection stratified by HBV-ICC, stone-ICC, and conventional ICC etiologic subtype. Of particular importance was the inclusion of patients from a multi-institutional experience that included both patients from Western and Eastern centers, as well as the use of PSM to compare patient cohorts. Of note, HBV-ICC tumors had markedly different clinicopathological characteristics compared with stone-ICC or conventional ICC. In addition,

patients with stone-ICC had a markedly shorter median OS compared with patients who had conventional ICC. In contrast, on PSM, patients with stone-ICC had equivalent RFS and OS versus patients who had HBV-ICC.

The finding that HBV-ICC patients were more likely have cirrhosis was not unexpected, as chronic HBV infection is a well-established risk factor for liver cirrhosis [27, 28]. In fact, HBV-ICC may have a similar underlying

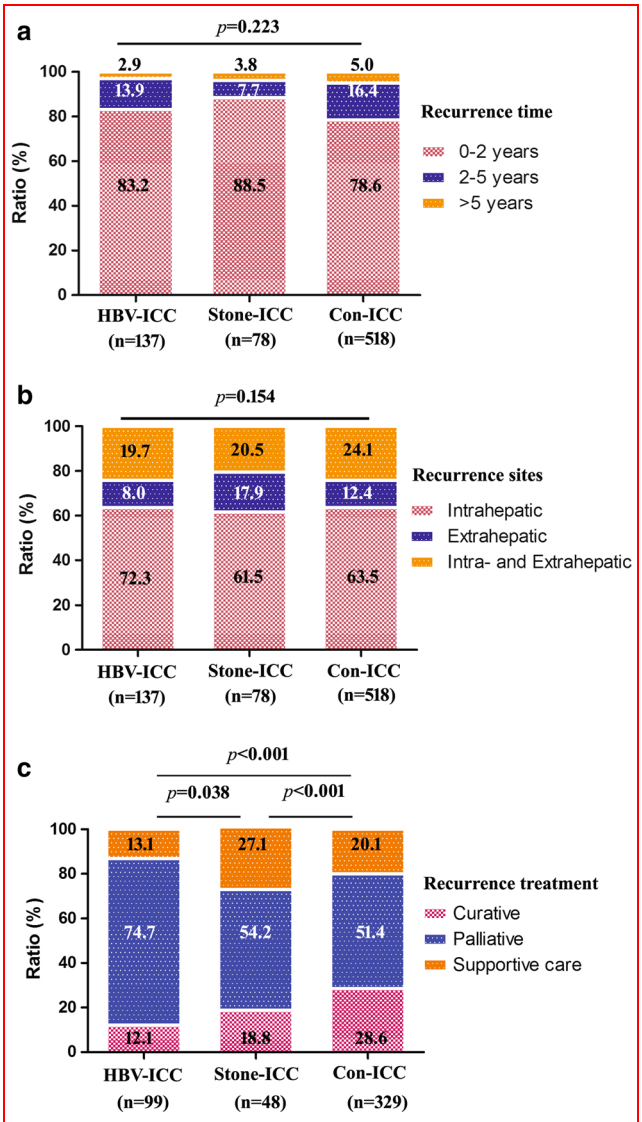

Fig. 3 The timing **a**, patterns **b** and treatments **c** of tumor recurrence after initial curative surgery in HBV-ICC, stone-ICC and conventional ICC groups. HBV, hepatitis B virus; ICC, intrahepatic cholangiocarcinoma; Con, conventional

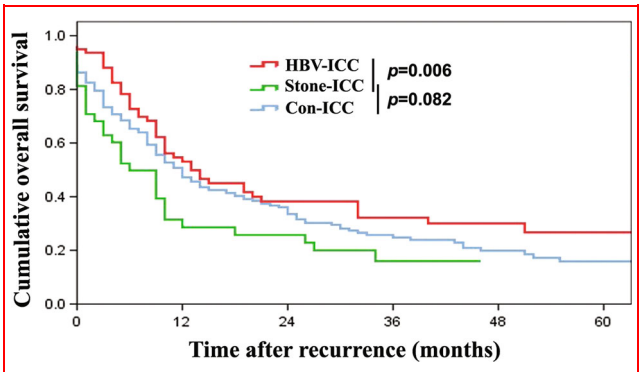

Fig. 4 Long-term survival calculated from the date of recurrence among patients with HBV-ICC, stone-ICC and conventional ICC. HBV, hepatitis B virus; ICC, intrahepatic cholangiocarcinoma; Con, conventional

pathogenesis as HBV-associated HCC [28, 29]. Like HCC, ICC can arise from any type of liver cell, including hepatic precursor cells and adult hepatocytes [29, 30]. In turn, HBV-HCC may be more likely to develop as a mass-forming lesion rather demonstrates the intra- or peri-ductal growth type, thereby emulating a histologically well-differentiated HCC [29–33]. Interestingly, HBV-ICC was more likely to present as an earlier stage tumor compared with either stone-ICC or conventional ICC. Specifically, HBV-ICC patients were less likely to have multiple tumors, bilateral disease, and lymph node metastases. HBV-ICC patients were also more likely have a mass-forming ICC that was moderately differentiated—features known to be associated with improved outcomes [16, 34–36]. In turn, perhaps not surprisingly, patients with HBV-ICC had better long-term outcomes compared with other etiological causes of ICC on standard survival analyses. However, after matching clinicopathological characteristics on PSM, patients with HBV-ICC had a comparable survival to patients who had stone-ICC. While the reasons for this are undoubtedly multi-factorial, the data strongly suggest that stage-for-stage survival of patients with HBV-ICC versus stone-ICC was not different. Rather, the finding that HBV patients had a better outcome on unadjusted survival analysis may instead be related to earlier ICC detection. This earlier detection may have been due to more frequent standard surveillance typically performed for patients with chronic liver disease.

Some previous studies had suggested that stone-ICC was more often diagnosed at advanced stages due to difficulties in differentiating this subtype of ICC from benign biliary strictures [16]. Other studies, however, had reported increased resectability for stone-ICC versus non-stone-ICC due to earlier diagnosis secondary to the presence of hepatolithiasis-associated symptoms [37–39]. In the current study, we noted that patients who had stone-ICC were comparable to patients who presented with conventional ICC and did not tend to present at later stages. Interestingly, patients with stone-ICC were noted to have a worse OS compared with patients who had conventional ICC both before and after PSM. In addition, patients who developed intrahepatic-only recurrence after initial surgery for stone-ICC were unlikely to be candidates of second curative-intent treatments for recurrent disease. In turn, stone-ICC patients had a more dismal post-recurrence survival than patients who experienced intrahepatic-only recurrence after hepatic surgery for HBV-ICC or conventional ICC (Fig. 4). These data would suggest that tumor biology, rather than clinical characteristics, were contributing to the more

aggressive nature of stone-ICC. Consistent with this hypothesis, stone-ICC has been reported to have more often a bile-duct pattern similar to hilar cholangiocarcinoma [40]. Furthermore, HBV-ICC demonstrates less *KRAS* mutations and more frequent *IDH1* and *IDH2* mutations, which are associated with DNA hypermethylation, prolonged time to recurrence, and improved survival [41]. In contrast, activation of human epidermal growth factor receptor 2 signaling has been more frequently identified in stone-ICC, which might partially account for the worse prognosis for this subtype of ICC [16, 42].

The current study had several limitations. The study included many centers from around the world. While this increased the generalizability of the study, certain factors such as the indication for resection, nuances of surgical technique, and perioperative management of patients undoubtedly varied. In addition, data on the viral load and antiviral treatments of patients with HBV-ICC were not available. Moreover, while most ICC patients with an unknown cause of ICC likely had a "sporadic" conventional ICC, other possible etiologies of ICC such as PSC, PBC, smoking, alcoholic, or nonalcoholic steatohepatitis were not part of the database and therefore could not be included in the analyses.

In conclusion, data from this large multi-institutional study indicated that patients with HBV-ICC had more favorable tumor features. While HBV-ICC had better RFS and OS on unadjusted analyses, these differences were mitigated on PSM suggesting no stage-for-stage differences in outcomes compared with stone-ICC or conventional ICC. In contrast, while stone-ICC had similar tumor characteristics with conventional ICC, patients with stone-ICC had a worse RFS and OS. These data highlight the relative importance of ICC etiology relative to established clinicopathological factors in establishing the prognosis of patients undergoing resection of ICC. Future studies will need to define better the distinct underlying molecular pathogenesis associated with the varied etiologies of ICC to inform treatment and surveillance strategies.

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Compliance with ethical standards

Conflicts of interest We have no financial or commercial interests to disclose

References

1. Aljiffry M, Abdulelah A, Walsh M et al (2009) Evidence-based approach to cholangiocarcinoma: a systematic review of the current literature. J Am Coll Surg 208:134–147
2. Khan SA, Toledano MB, Taylor-Robinson SD (2008) Epidemiology, risk factors, and pathogenesis of cholangiocarcinoma. HPB (Oxford) 10:77–82
3. Saha SK, Zhu AX, Fuchs CS et al (2016) Forty-year trends in cholangiocarcinoma incidence in the US: intrahepatic disease on the rise. Oncologist 21:594–599
4. Shin HR, Oh JK, Masuyer E et al (2010) Comparison of incidence of intrahepatic and extrahepatic cholangiocarcinoma–focus on East and South-Eastern Asia. Asian Pac J Cancer Prev 11:1159–1166
5. Buettner S, van Vugt JL, IJ JN et al (2017) Intrahepatic cholangiocarcinoma: current perspectives. Onco Targets Ther 10:1131–1142
6. Brito AF, Abrantes AM, Encarnacao JC et al (2015) Cholangiocarcinoma: from molecular biology to treatment. Med Oncol 32:245
7. Dodson RM, Weiss MJ, Cosgrove D et al (2013) Intrahepatic cholangiocarcinoma: management options and emerging therapies. J Am Coll Surg 217(736–750):e734
8. Anderson CD, Pinson CW, Berlin J et al (2004) Diagnosis and treatment of cholangiocarcinoma. Oncologist 9(43–5):7
9. Ben-Menachem T (2007) Risk factors for cholangiocarcinoma. Eur J Gastroenterol Hepatol 19:615–617
10. Blechacz BR, Gores GJ (2008) Cholangiocarcinoma. Clin Liver Dis 12:131–150
11. Spolverato G, Vitale A, Cucchetti A et al (2015) Can hepatic resection provide a long-term cure for patients with intrahepatic cholangiocarcinoma? Cancer 121:3998–4006
12. Weber SM, Jarnagin WR, Klimstra D et al (2001) Intrahepatic cholangiocarcinoma: resectability, recurrence pattern, and outcomes. J Am Coll Surg 193:384–391
13. Amini N, Ejaz A, Spolverato G et al (2014) Temporal trends in liver-directed therapy of patients with intrahepatic cholangiocarcinoma in the United States: a population-based analysis. J Surg Oncol 110:163–170
14. Mavros MN, Economopoulos KP, Alexiou VG et al (2014) Treatment and prognosis for patients with intrahepatic cholangiocarcinoma: systematic review and meta-analysis. JAMA Surg 149:565–574
15. Spolverato G, Kim Y, Alexandrescu S et al (2016) Management and outcomes of patients with recurrent intrahepatic cholangiocarcinoma following previous curative-intent surgical resection. Ann Surg Oncol 23:235–243
16. Wang Q, Li J, Lei Z et al (2017) Prognosis of intrahepatic cholangiocarcinomas with HBV infection is better than those with hepatolithiasis after R0 liver resection: a propensity score matching analysis. Ann Surg Oncol 24:1579–1587
17. Ahn CS, Hwang S, Lee YJ et al (2016) Prognostic impact of hepatitis B virus infection in patients with intrahepatic cholangiocarcinoma. ANZ J Surg. doi:10.1111/ans.13753
18. Zhang L, Cai JQ, Zhao JJ et al (2010) Impact of hepatitis B virus infection on outcome following resection for intrahepatic cholangiocarcinoma. J Surg Oncol 101:233–238
19. Wakabayashi H, Hashimoto N, Okano K et al (2008) Clinicopathological comparison between intrahepatic cholangiocarcinoma arising in livers positive and negative for hepatitis B or C virus. Liver Int 28:717–718
20. Horino K, Beppu T, Komori H et al (2012) Evaluation of mass-forming intrahepatic cholangiocarcinoma with viral hepatitis. Hepatogastroenterology 59:1217–1219
21. Ariizumi S, Kotera Y, Takahashi Y et al (2011) Mass-forming intrahepatic cholangiocarcinoma with marked enhancement on arterial-phase computed tomography reflects favorable surgical outcomes. J Surg Oncol 104:130–139
22. Su CH, Shyr YM, Lui WY et al (1997) Hepatolithiasis associated with cholangiocarcinoma. Br J Surg 84:969–973

23. Chen MF, Jan YY, Jeng LB et al (1999) Intrahepatic cholangiocarcinoma in Taiwan. J Hepatobiliary Pancreat Surg 6:136–141
24. Liu RQ, Shen SJ, Hu XF et al (2013) Prognosis of the intrahepatic cholangiocarcinoma after resection: hepatitis B virus infection and adjuvant chemotherapy are favorable prognosis factors. Cancer Cell Int 13:99
25. Edge SBD, Compton CC, Fritz AG, Greene FL (2010) Trotti A AJCC Cancer Staging Manual, 7th edn. Springer, New York
26. Chang KY, Chang JY (2009) Yen Y Increasing incidence of intrahepatic cholangiocarcinoma and its relationship to chronic viral hepatitis. J Natl Compr Canc Netw 7:423–427
27. El-Serag HB (2012) Epidemiology of viral hepatitis and hepatocellular carcinoma. Gastroenterology 142(1264–1273):e1261
28. Zhou H, Wang H, Zhou D et al (2010) Hepatitis B virus-associated intrahepatic cholangiocarcinoma and hepatocellular carcinoma may hold common disease process for carcinogenesis. Eur J Cancer 46:1056–1061
29. Palmer WC (2012) Patel T Are common factors involved in the pathogenesis of primary liver cancers? A meta-analysis of risk factors for intrahepatic cholangiocarcinoma. J Hepatol 57:69–76
30. Sekiya S (2012) Suzuki A Intrahepatic cholangiocarcinoma can arise from Notch-mediated conversion of hepatocytes. J Clin Invest 122:3914–3918
31. Wilkens L, Bredt M, Flemming P et al (2000) Differentiation of multicentric origin from intra-organ metastatic spread of hepatocellular carcinomas by comparative genomic hybridization. J Pathol 192:43–51
32. Vijgen S, Terris B (2017) Rubbia-Brandt L Pathology of intrahepatic cholangiocarcinoma. Hepatobiliary Surg Nutr 6:22–34
33. Zhou XD, Tang ZY, Fan J et al (2009) Intrahepatic cholangiocarcinoma: report of 272 patients compared with 5829 patients with hepatocellular carcinoma. J Cancer Res Clin Oncol 135:1073–1080
34. Wu ZF, Yang N, Li DY et al (2013) Characteristics of intrahepatic cholangiocarcinoma in patients with hepatitis B virus infection: clinicopathologic study of resected tumours. J Viral Hepat 20:306–310
35. Bagante F, Spolverato G, Weiss M et al (2017) Impact of morphological status on long-term outcome among patients undergoing liver surgery for intrahepatic cholangiocarcinoma. Ann Surg Oncol 24:2491–2501
36. Shirabe K, Mano Y, Taketomi A et al (2010) Clinicopathological prognostic factors after hepatectomy for patients with mass-forming type intrahepatic cholangiocarcinoma: relevance of the lymphatic invasion index. Ann Surg Oncol 17:1816–1822
37. Chen MF, Jan YY, Hwang TL et al (2000) Impact of concomitant hepatolithiasis on patients with peripheral cholangiocarcinoma. Dig Dis Sci 45:312–316
38. Guglielmi A, Ruzzenente A, Valdegamberi A et al (2014) Hepatolithiasis-associated cholangiocarcinoma: results from a multi-institutional national database on a case series of 23 patients. Eur J Surg Oncol 40:567–575
39. Lee CC, Wu CY, Chen GH (2002) What is the impact of coexistence of hepatolithiasis on cholangiocarcinoma? J Gastroenterol Hepatol 17:1015–1020
40. Liau JY, Tsai JH, Yuan RH et al (2014) Morphological subclassification of intrahepatic cholangiocarcinoma: etiological, clinicopathological, and molecular features. Mod Pathol 27:1163–1173
41. Wang P, Dong Q, Zhang C et al (2013) Mutations in isocitrate dehydrogenase 1 and 2 occur frequently in intrahepatic cholangiocarcinomas and share hypermethylation targets with glioblastomas. Oncogene 32(25):3091
42. Sia D, Hoshida Y, Villanueva A et al (2013) Integrative molecular analysis of intrahepatic cholangiocarcinoma reveals 2 classes that have different outcomes. Gastroenterology 144:829–840